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(54) Title: METHOD FOR INCORPORATION OF PENTAFLUOROSULFANYL (SF_5) SUBSTITUENTS INTO ALIPHATIC AND AROMATIC COMPOUNDS

(57) Abstract: The subject invention provides convenient, regiospecific and highly stereoselective addition of SF_5Cl in high yield to a variety of alkenes and alkynes.

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DESCRIPTION

METHOD FOR INCORPORATION OF PENTAFLUOROSULFANYL (SF_5) SUBSTITUENTS INTO ALIPHATIC AND AROMATIC COMPOUNDS

The subject invention was made with government support under a research project supported by the Air Force Office of Scientific Research, STTR Phase I Contract #F49620-01-C-0046. The United States government may have certain rights in this invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/448,831, filed February 21, 2003, and also claims the benefit of U.S. Provisional Application Serial No. 60/399,044, filed July 25, 2002.

BACKGROUND OF INVENTION

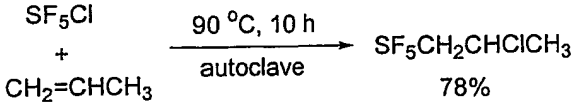
[0002] There is currently great interest in methods for the preparation of selectively fluorinated organic compounds. This interest results from the profound influence that fluorine incorporation can have on the physical properties, chemical properties, and biological activity of molecules. For example, methods for putting the bulky, highly electronegative and generally inert trifluoromethyl group into organic compounds have received much research attention during recent years.

[0003] Another fluorinated substituent that could attract interest among synthetic organic chemists is the pentafluorosulfanyl (SF_5) group (Winter *et al.*, *Inorganic Fluorine Chemistry - Toward the 21st Century* (1994) 555:128-47, Pub: American Chemical Society: Washington (Thrasher, J. S., Strauss, S. H., Eds.); Lentz *et al.*, *Chemistry of Hypervalent Compounds* (1999) 295-326; Pub: Wiley-VCH: New York (Akiba, K., Ed.); Verma *et al.*, *Advances in Inorganic Chemistry* (1994) 41:125-69, Pub: Academic Press: San Diego (Sykes, A. G., Ed.); pentafluorosulfanyl groups bear some similarity to trifluoromethyl

groups, however, SF_5 is more electronegative (σ_p = +0.68 versus +0.54 for CF_3; Sheppard, W. A., *J. Am. Chem. Soc.* (1962) 84:3072-6) and more sterically demanding.

[0004] However, until the development of the subject invention, methods for the addition of an SF_5 substituent to a benzene ring or other aliphatic compounds were inconvenient, dangerous, and many methods required the use of elemental F_2 or oxidative fluorination by AgF_2 (Sheppard, W. A., *J. Am. Chem. Soc.* (1962) 84:3064-3072; Chambers *et al.*, *Chem. Commun.* (1999) 883-884; Bowden *et al.*, *Tetrahedron* (2000) 56:3399-3408; Sipyagin *et al.*, *J. Fluorine Chem.* (2001) 112:287-295) to incorporate an SF_5 group into aliphatic compounds (*i.e.*, the methodologies relied on high pressure autoclave or specialized photochemical procedures) (Case *et al.*, *J. Chem. Soc.* (1961) 2066-2070; Wessel *et al.*, *Chem. Ber.* (1983) 116:2399-2407; Winter *et al.*, *J. Fluorine Chem.* (1994) 66:109-116; Fokin *et al.*, *Russ. Chem. Bull.* (1996) 45:2804-6). Thus, the introduction SF_5 into aliphatic compounds has not been widely practiced by synthetic organic chemists.

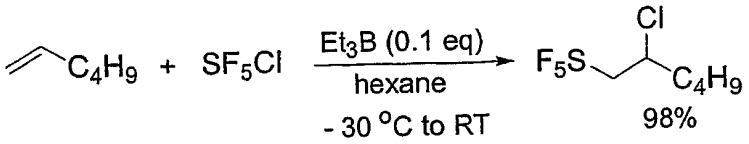
[0005] SF_5Cl is presently the only commercially available "reagent" that can be used to introduce the SF_5 substituent into aliphatic compounds. As a gaseous pseudo halogen, this reagent cannot be used as an electrophilic source of SF_5. It has, however, been used in free radical chain alkene/alkyne addition processes (Sidebottom *et al.*, *Trans. Faraday Soc.* (1969) 65:2103-2109). These processes are generally done thermally, in an autoclave, with or without an initiator, or using room temperature gas phase or low temperature solution phase photochemical processes. For example (Case *et al.*, *J. Chem. Soc.* (1961) 2066-2070):



[0006] In order for SF_5-derivatives to become incorporated into the day-to-day strategic planning of working synthetic organic chemists, a convenient bench-top procedure for the introduction of SF_5 substituents into organic substrates is needed. The subject invention provides such a method – one that will allow convenient addition of SF_5Cl to a large variety of aliphatic compounds (such as alkenes and alkynes) in excellent yield.

BRIEF SUMMARY

[0007] The subject invention provides methods for the convenient addition of pentafluorosulfanyl substituents into aliphatic organic compounds. In various embodiments, pentafluorosulfanyl substituents are incorporated into pharmaceutical compounds or agrochemical compounds containing aliphatic groups. An exemplary reaction is:



DETAILED DISCLOSURE

[0008] The subject invention provides methods for the convenient addition of pentafluorosulfanyl substituents into aliphatic organic compounds. In various embodiments, pentafluorosulfanyl substituents are incorporated into pharmaceutical compounds or agrochemical compounds containing aliphatic groups. The invention also provides aromatic SF_5 substituted compounds and methods of preparing such compounds comprising the addition of SF_5Cl to cyclohexene and cyclohexadiene derivatives followed by elimination/oxidation steps.

[0009] The simplicity of new method provided by the subject invention, combined with the generally excellent yields that are obtained, constitutes a breakthrough in SF_5 synthetic methodology that opens the door to the convenient, bench top preparation of a multitude of SF_5-containing aliphatics by synthetic organic chemists. Thus, the subject invention has application to broad applicability to any compound containing aliphatic groups, including functionalized or substituted compounds.

[0010] Exemplary compounds into which pentafluorosulfanyl substituents can be incorporated include those compounds containing one or more functional groups selected from the group consisting of substituted or unsubstituted aliphatic groups, substituted or unsubstituted aromatic groups, substituted or unsubstituted alicyclic groups, substituted or unsubstituted alkene groups, substituted or unsubstituted alkyne groups, substituted or unsubstituted styrene groups, disubstituted alkene groups (*e.g.*, 2,2-disubstituted alkenes), substituted or unsubstituted non-terminal alkene groups, substituted or unsubstituted non-

terminal alkyne groups, cyclohexene groups, substituted cyclohexene groups, cyclohexadiene groups, substituted cyclohexadiene groups, and combinations of such functional groups, or derivatives of the aforementioned functional groups. These compounds may also be referred to as compounds of interest within this specification.

[0011] In various embodiments, pharmaceutical compounds or agrochemical compounds (*e.g.*, herbicides, insecticides, pesticides, vermin poisons) comprising one or more aliphatic, aromatic, alicyclic, alkene, alkyne, styrene, disubstituted alkene, non-terminal alkene, or non-terminal alkyne functional groups can be treated according to the subject process to incorporate pentafluorosulfanyl substituents into their respective structures. The mildness of the alkylborane, dialkylborane, trialkylborane, and/or 9-borabicyclo[3.3.1]nonane-catalyzed reaction conditions contributes to the broad applicability of the methods provided by the subject invention.

[0012] With a boiling point of -21°C, SF_5Cl is readily condensed into hexane which, in some embodiments, contains the aliphatic, aromatic, alicyclic, alkene, or alkyne substrate of interest. When an initiator or catalyst is added (*e.g.*, by syringe), an immediate reaction is evident, and, for many substrates, the reaction is effectively complete after 30 minutes. Initiators/catalysts suitable for use in the subject invention include alkylboranes, dialkylboranes, trialkylboranes, and/or 9-borabicyclo[3.3.1]nonane; alternatively, one or more initiators/catalysts (*e.g.*, various combinations of the aforementioned initiators/catalysts) can be used in the methods taught herein. The terms initiator and catalyst may be used interchangeably in the context of the subject invention. Solutions containing SF_5Cl and/or compounds of interest can be maintained at temperatures of about -20°C to -40°C, -30°C to -40°C, or -20°C to -30°C.

[0013] Thus, the subject invention provides novel pentafluorosulfanyl substituted compounds and methods of making pentafluorosulfanyl substituted compounds. The subject invention also provides for the production of SF_5Cl compounds that have been enantiomerically enriched according to methods known in the art. Substituted compounds according to the subject invention can be made by adding of SF_5Cl to hexane to form a SF_5Cl containing hexane solution, contacting a hexane solution comprising one or more compounds of interest containing one or more functional groups selected from the group consisting of substituted or unsubstituted aliphatic groups, substituted or unsubstituted aromatic groups,

substituted or unsubstituted alicyclic groups, substituted or unsubstituted alkene groups, substituted or unsubstituted alkyne groups, substituted or unsubstituted styrene groups, disubstituted alkene groups (*e.g.*, 2,2-disubstituted alkenes), substituted or unsubstituted non-terminal alkene groups, substituted or unsubstituted non-terminal alkyne groups, cyclohexene groups, substituted cyclohexene groups, cyclohexadiene groups, substituted cyclohexadiene groups, and combinations of such functional groups, or derivatives of the aforementioned functional groups, with the SF_5Cl hexane solution, and adding one or more catalyst(s)/initiator(s) selected from the group consisting of dialkylboranes, trialkylboranes, and 9-borabicyclo[3.3.1] nonane. The reactants are mixed and maintained under conditions suitable for the addition of pentafluorosulfanyl substituents to the compounds of interest. The reaction can be terminated at any point, however, allowing the reaction to proceed to completion results in increased yields of SF_5-substituted compounds. In embodiments where cyclohexenes (or derivatives thereof) and/or cyclohexadienes (or derivatives thereof) are substituted with SF_5Cl, elimination/oxidation steps may be used to form SF_5 aromatics.

[0014] Pentfluorosulfanyl substituted compounds may, optionally, be hydrolyzed and, optionally, dried over a suitable desiccant. The pentfluorosulfanyl substituted compounds can then, optionally, be passed over a short column (containing, for example, a sizing gel or silica gel) to remove contaminants (such as, for example, catalyst/initiator or unsubstituted compounds). Purity and/or analysis of the pentafluorosulfanyl substituted compounds of the invention can be determine using methods well-known to those skilled in the art, including, and not limited to, NMR analysis. In various embodiments, the catalyst(s)/initiator(s) may be added to one or more of a hexane solution containing SF_5Cl or a hexane solution containing one or more compounds of interest prior to the combination of these hexane solutions.

[0015] Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1 – SF_5 Substituted Alkene Compounds

[0016] Into a three-necked flask equipped with a dry ice reflux condenser and a nitrogen inlet were added (at - 40°C) 15 mL of anhydrous hexane, alkene (3-4 mmol) and SF_5Cl (1.2 equiv). The solution was stirred at this temperature for 5 minutes and then Et_3B (0.1 equiv, 1M in hexane) was added slowly using a syringe. The solution was vigorously

stirred for 1 hour at -30°C to -20°C, and then the mixture was allowed to warm to room temperature.

[0017] The mixture was hydrolyzed with aqueous $NaHCO_3$ (10%) and the organic layer dried over $MgSO_4$. The solvent was removed and the crude product was passed through a short column of silica gel, eluting with CH_2Cl_2. Removal of solvent in most cases provided the products in essentially pure form without the need for additional purification. The reaction can be worked up by simple evaporation of the hexane to give, in most cases, essentially pure product. No significant impurities are observed by ^1H, ^{19}F, or ^{13}C NMR; however, optional passage through a short column may be used to eliminate, or reduce, possible traces amounts of Et_3B.

[0018] Table 1 gives the yields for addition of SF_5Cl to a variety of alkenes. Table 2 gives the results for addition to three typical alkynes. Products containing the SF_5 substituent are readily confirmed by the presence of the characteristic AB_4 pair of pentuplet and doublet signals in their ^{19}F NMR spectra, which along with their ^1H and ^{13}C spectra allowed unambiguous characterization of all of the products.

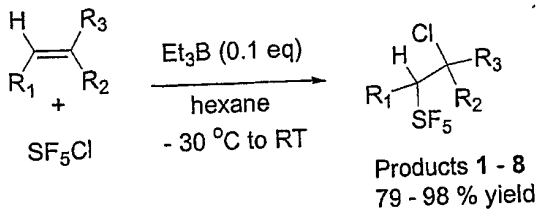
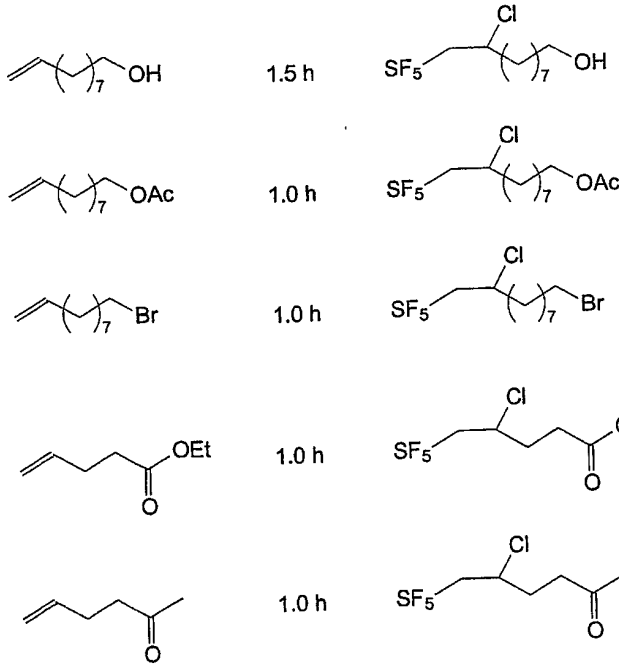


Table 1. Yields for addition of SF_5Cl to alkenes[a]

R_1	R_2	R_3	Product, (% yield)
H	n-C_6H_{13}	H	**1**, 95
H	n-C_4H_9	H	**2**, 98 [19]
H	t-C_4H_9	H	**3**, 96
H	C_2H_5	C_2H_5	**4**, 89
n-C_3H_7	H	n-C_3H_7	**5**, 95[b]
$(CH_2)_4$		H	**6**, 98[b, 11]
H	p-tolyl	H	**7**, 79
H	OAc	H	**8**. 98 [20]

[a] in hexane, at – 30 °C, 0.1 equiv. Et_3B, 30 minutes
[b] one major diastereomer (> 90% by NMR)

Other examples include, but are not limited to:



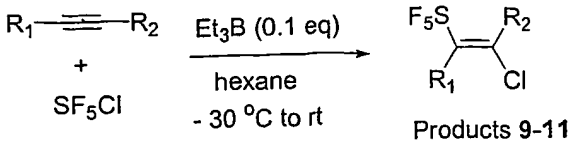
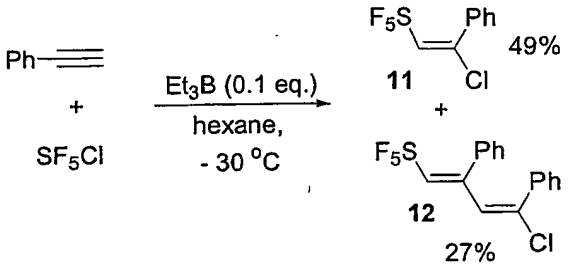


Table 2. Addition of SF_5Cl to Alkynes[a]

R_1	R_2	Product,[b] % yield
n-C_3H_7	n-C_3H_7	**9**, 93
H	n-C_6H_{13}	**10**, 94
H	Ph	**11**, 94 + **12**, 27

[a] in hexane, at – 30 °C, 0.1 equiv. Et_3B, 30 minutes
[b] Single diastereomer in each case.

In the reaction with phenyl acetylene, a 2:1 adduct was also obtained in 27% yield. In this case, addition of the propagating radical intermediate to a



second phenyl acetylene is obviously competing with the chain transfer step. Using a larger excess of SF_5Cl in the reaction can minimize this 2:1 product.

The addition reactions are regiospecific and highly diastereoselective, with essentially one product being formed from the additions to cyclohexene, *trans*-4-octene and the alkynes. Many of the alkyne adducts are novel, although the SF_5Cl adduct of propyne has been reported. (Case *et al.*, *J. Chem. Soc.* (1961) 2066-2070.) Although many of the alkene adducts have been reported previously (Case *et al.*, *J. Chem. Soc.* (1961) 2066-2070; Winter *et al.*, *J. Fluorine Chem.* (2001) 107:23-30), styrenes, 2,2-disubstituted alkenes, and non-terminal alkenes had not previously proved to be good substrates for SF_5Cl addition.

Example 2- SF_5 Substituted Aromatic/Alicyclic Compounds

[0019] SF_5Cl was added to 1,3 cyclohexadiene under the conditions described in Example 1. The resulting adduct was treated with $KmnO_4/Al_2O_3$ powder (1:1 (w/w)) for two hours at 0°C. SF_5 benzene was then recovered in yields of about 60%. In alternative embodiments, substituted cyclohexadienes, or substituted cyclohexenes, can act as substrates in the SF_5CL addition reaction. These adducts can, then, be subjected to eliminative or oxidative chemistry to form SF_5 aromatics.

Example 3 – Novel Two-Step Synthesis of Pentafluorosulfanylbenzene

[0020] 1. Synthesis of 1-pentafluorosulfanyl-2, 4, 5-trichloro-cyclohexane: A three-necked round bottom flask equipped with a dry ice reflux condenser and a nitrogen inlet was charged with 4,5-dichloro-1-cyclohexane (2.1 g, 0.014M) and 25 mL of dry CH_2Cl_2. The mixture was cooled to -60°C and SF_5Cl (8.4g, 0.042M, 3.7 eq.) was added. One and one-half (1.5) mL of a Et_3B solution (1M solution in hexane, 0.1 eq.) was slowly added to the mixture using a syringe. Temperature was slowly increased to -30°C and the mixture was stirred at -30° to -20°C for four hours. The solvent was evaporated, furnishing an essentially pure product (4.14g, 0.013M) in a yield of about 94%. The product had the following characteristics: ^1H NMR spectrum ($CDCl_3$, 300 MHz): 4.7 (broad singlet, 1H, CH-SF_5), 4.4-4.15 (m, 3H, CHCl), 3-2.4 (m, 4H, CH_2); and ^{19}F NMR spectrum ($CDCl_3$): 82.9 (m,1F), 57.9 (broad d, 4F).

[0021] 2. Synthesis of pentafluorosulfanylbenzene: A 100-mL round bottom flask equipped with a water condenser was charged with 1-pentafluorosulfanyl-2, 4, 5-trichlorocyclohexane (4.1g, 0.012M) and 60 mL of NaOEt (1.59M solution). The mixture was vigorously stirred at ambient temperature overnight. Water was added, and the solution was extracted with CH_2Cl_2. The extract was washed with water (3 times) and dried over $MgSO_4$. Evaporation of the solvent furnished a mixture of a liquid and a white solid. The solid was filtered off, leaving pentafluorosulfanylbenzene (1.95 g, ca. 0.01M) in a yield of about 79%. Overall yield calculated from 4, 5-dichloro-1-cyclohexene: about 71%. The product had the following characteristics: ^1H NMR spectrum ($CDCl_3$, 300 MHz): 7.7 (m, 2H) and 7.5 (m, 3H); and ^{19}F NMR spectrum ($CDCl_3$): 84.6 (q,1F), 62.8 and 62.4 (4F).

[0022] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

[0023] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

CLAIMS

We claim:

1. A method of making pentafluorosulfanyl substituted compounds comprising the steps of:

a) contacting a hexane solution comprising one or more compounds comprising one or more functional groups selected from the group consisting of substituted or unsubstituted aliphatic groups, substituted or unsubstituted aromatic groups, substituted or unsubstituted alicyclic groups, substituted or unsubstituted alkene groups, substituted or unsubstituted alkyne groups, substituted or unsubstituted styrene groups, disubstituted alkene groups (*e.g.*, 2,2-disubstituted alkenes), substituted or unsubstituted non-terminal alkene groups, substituted or unsubstituted non-terminal alkyne groups, cyclohexene groups, substituted cyclohexene groups, cyclohexadiene groups, substituted cyclohexadiene groups, and combinations of such functional groups, or derivatives of the aforementioned functional groups, with a SF_5Cl hexane solution;

b) adding one or more catalyst(s)/initiator(s) selected from the group consisting of dialkylboranes, trialkylboranes, 9-borabicyclo[3.3.1] nonane, and mixtures thereof; and

c) allowing the reaction of said compounds and said SF_5CL solution to proceed under conditions suitable for the addition of pentafluorosulfanyl substituents to said compounds.

2. The method according to claim 1, wherein the reaction is allowed to proceed to completion.

3. The method according to claim 1, further comprising an elimination or oxidation step.

4. The method according to claim 1, further comprising a hydrolysis step.

5. The method according to claim 4, further comprising a drying step.

6. The method according to claim 5, wherein said drying step is performed over a dessicant.

7. The method according to claim 1, further comprising a purification step.

8. The method according to claim 2, further comprising a purification step.

9. The method according to claim 3, further comprising a purification step.

10. The method according to claim 4, further comprising a purification step.

11. The method according to claim 5, further comprising a purification step.

12. The method according to claim 1, wherein the catalyst(s)/initiator(s) are added to: 1) a hexane solution containing SF_5Cl; or 2) a hexane solution containing one or more compounds prior to the combination of the solution containing SF_5CL and the solution containing a compound.

13. A method of making pentafluorosulfanyl benzene comprising the steps of:

a) mixing 4,5-dichloro-1-cyclohexane, CH_2Cl_2, SF_5Cl, and a catalyst selected from the group consisting of dialkylboranes, trialkylboranes, 9-borabicyclo[3.3.1] nonane, and mixtures thereof;

b) evaporating the solvent from the mixture of step a) and recovering the product produced thereby;

c) contacting the product obtained in step b) with a solution of sodium ethoxide (NaOEt);

d) adding water to the solution of step c) and extracting said solution;

e) washing the extract of step d) and drying the extract over a dessicant;

f) allowing solvent evaporation from the extract of step e); and

g) recovering pentafluorosulfanylbenzene from the extract of step f).

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US 03/24836

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C381/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 891 552 A (IMPERIAL CHEMICAL INDUSTRIES LTD) 14 March 1962 (1962-03-14) the whole document	1,2,7,8
A	GB 907 648 A (IMPERIAL CHEMICAL INDUSTRIES LTD) 10 October 1962 (1962-10-10) the whole document	1,2,7,8
A	US 3 102 903 A (D.D. COFFMAN ET AL) 3 September 1963 (1963-09-03) examples I-III; column 7, line 54 - column 8, line 6	1,2,4,7, 8,10
A	GB 905 006 A (IMPERIAL CHEMICAL INDUSTRIES LTD) 5 September 1962 (1962-09-05) the whole document	1,3,9,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2003	26/11/2003

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INTERNATIONAL SEARCH REPORT

Intern: l Application No
PCT/US 03/24836

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	W.A. SHEPPARD: J. AMC. CHEM. SOC., vol. 84, 1962, pages 3064-3072, XP002261211 cited in the application page 3070, column 1	13
P,X	S. AÏT-MOHAND ET AL: ORG. LETT., vol. 4, no. 17, 2002, pages 3013-3015, XP002261212 the whole document	1,2,7,8, 12

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INTERNATIONAL SEARCH REPORT

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			NL	255510 A	
GB 907648	A	10-10-1962	NONE		
US 3102903	A	03-09-1963	NONE		
GB 905006	A	05-09-1962	NONE		